CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

CALCITONIN GENE–RELATED PEPTIDE ENHANCES THE RECOVERY OF CONTRACTILE FUNCTION IN STUNNED MYOCARDIUM

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Introduction: Calcitonin gene-related peptide, a potent vasodilating inotropic agent, increases coronary artery perfusion when administered exogenously and reduces ischemic injury in nonmyocardial tissue. However, it is unclear whether this agent improves recovery of myocardial performance after reversible myocardial ischemia.

Methods: Nine dogs underwent complete occlusion of the left anterior descending coronary artery for 15 minutes and were monitored during 24 hours of reperfusion. Calcitonin gene–related peptide (0.07 μg · kg^{-1} · min^{-1}), nitroglycerin (65 μg · kg^{-1} · min^{-1}), or saline solution placebo was infused intravenously during initial reperfusion. Ischemia/reperfusion was repeated in concurrent 24-hour periods until all animals received infusions in random order. Micromanometry and sonomicrometry determined left ventricular pressure and myocardial segment length. Myocardial performance, based on the linear relationship between stroke work and end-diastolic segment length, was estimated with the preload recruitable work area. Results were analyzed as percent control and compared statistically with the use of repeated measures analysis of variance.

Results: Recovery of myocardial performance was augmented during reperfusion with calcitonin gene–related peptide infusion relative to placebo (P = .005; mean preload recruitable work area ± SE after calcitonin gene–related peptide infusion, 2484 ± 705 mm Hg at 90 minutes of reperfusion versus 1473 ± 300 mm Hg for placebo. Recovery of performance after nitroglycerin infusion was similar to recovery after placebo.

Conclusions: Calcitonin gene–related peptide infusion improves recovery of contractile function in stunned myocardium. Unlike inotropic agents that impair recovery from reversible ischemia, calcitonin gene–related peptide may confer cardioprotective effects on ischemic myocardium. (J Thorac Cardiovasc Surg 2000;119:1246-54)

Early myocardial reperfusion is a primary goal in treating acute myocardial ischemia and is commonplace with thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass procedures. However, early reperfusion is complicated by myocardial stunning or reversible dysfunction.[1,2] Myocardial stunning is encountered after most cardiac operations, cardiac transplantation, and cardiopulmonary arrest and after less clinically obvious episodes of reversible myocardial ischemia.[1] However, consequences of stunned myocardium are often prevented by vasoactive medications. Still, it is proposed that prevention of myocardial stunning may improve the clinical course after reversible myocardial ischemia. To date, few therapies are proved to augment the recovery of myocardial performance within stunned myocardium without the induction of deleterious effects.[3]

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Calcitonin gene–related peptide (CGRP) is a vasoactive protein found in cardiac slow-conducting c-fiber afferents, and CGRP receptors are widely distributed throughout the myocardium and vascular system.[4] Functionally, CGRP is a potent endogenous vasodilator and exerts chronotropic and inotropic effects directly on the myocardium.[5,6] Because of these vasodilatory properties, elevated concentrations of CGRP that are observed in regional tissue and in plasma after transient myocardial ischemia could have beneficial effects.[7-9]

Recognizing these unique properties, investigators have recently evaluated exogenous CGRP in ischemia. For instance, CGRP administration may improve tissue viability and functional recovery in ischemic skeletal muscle.[10-12] In addition, CGRP administration delayed the onset of ischemia in patients with coronary artery disease who were subjected to exercise treadmill testing.[13] Despite these findings, few data describe the effect of exogenous CGRP administration on indices of myocardial performance after reversible myocardial ischemia. Therefore, this study was undertaken to assess the ability of CGRP to augment recovery of contractile function within stunned myocardium in a canine model of regional myocardial ischemia.

Methods

Experimental preparation. All experiments were conducted in accordance with guidelines published in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985) and under protocols approved by Duke University. Nine dogs (20-25 kg) were premedicated with pentobarbital sodium (25 mg/kg, intravenously) and fentanyl citrate (10-20 μg/kg, intravenously), intubated, and mechanically ventilated (Puritan-Bennett Corp, Medical Products Division, Los Angeles, Calif). A sterile thoracotomy in the fifth left intercostal space exposed the heart, and pneumatic occluders were secured around the superior and inferior venae cavae. After pericardiotomy, a silicone rubber pneumatic occluder was placed around the left anterior descending (LAD) coronary artery distal to the first diagonal branch. A brief test occlusion identified the myocardial region rendered ischemic (Fig 1). One pair of piezoelectric dimension transducers was implanted intramyocardially in the ischemic left ventricular (LV) region. A second pair of dimension transducers was placed in the distribution of the left circumflex (LCX) coronary artery to assess nonischemic myocardium (Fig 1). Silicone rubber catheters were implanted in left atrium and pleural space to allow subsequent placement of pressure transducers in these spaces. Implanted hardware were brought through a separate rib space and through a silicone rubber skin appliance positioned dorsal to the thoracotomy incision. The thoracotomy was closed in layers, and animals were allowed to recover for 2 weeks.

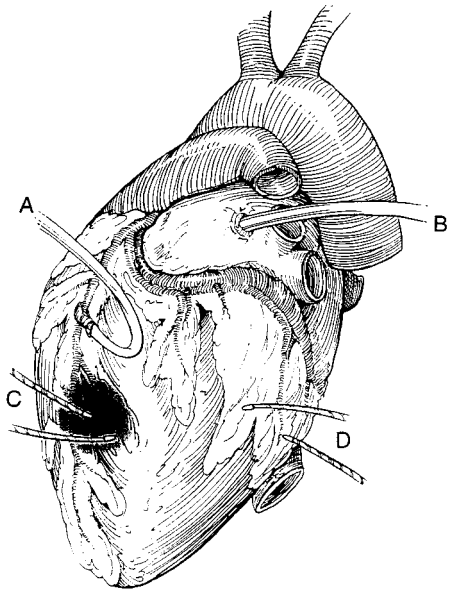

Fig 1. Experimental preparation shows the pneumatic occluder secured around the LAD coronary artery *(A)*, left atrial introducer catheter *(B)*, intramyocardial ultrasonic dimension transducer pair in the ischemic (*darkened area*) LAD coronary artery region *(C)*, and ultrasonic dimension transducer pair in the LCX coronary artery distribution *(D)*. Implanted pleural catheters and vena caval pneumatic occluders are not shown.

Data acquisition. Each dog was studied in the conscious state after mild sedation (morphine sulfate, 0.7-1.0 mg/kg, intramuscularly). Dimension transducer pairs were coupled to a sonomicrometer with a sampling rate of 250 Hz and a frequency response up to 50 Hz. Micromanometers (model PC-500; Millar Instruments, Inc, Houston, Tex) were positioned in the LV cavity and pleural space with implanted silicone rubber catheters.

Intravenous heparin sodium (300 units/kg) and lidocaine (2 mg/kg) were administered, and baseline physiologic data were recorded. The pneumatic LAD coronary artery occluder was fully inflated for 15 minutes, and standard electrocardiogram leads and myocardial segment lengths were monitored to verify myocardial ischemia. Animals were observed during 45 minutes of reperfusion, after which each animal received intravenous CGRP (0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$; Peninsula Laboratory, San Jose, Calif), nitroglycerin (65 $\mu g \cdot kg^{-1} \cdot min^{-1}$), or saline solution placebo infusion for 1 hour. Data were collected at steady state and across altered loading conditions produced by vena caval occlusion at baseline, during acute ischemia, and after 1.5, 3, 8, and 24 hours of reperfusion. The initial data collection during drug infusion was begun at 1.5 hours of reperfusion to allow 30 minutes of drug infusion to achieve steady state conditions.

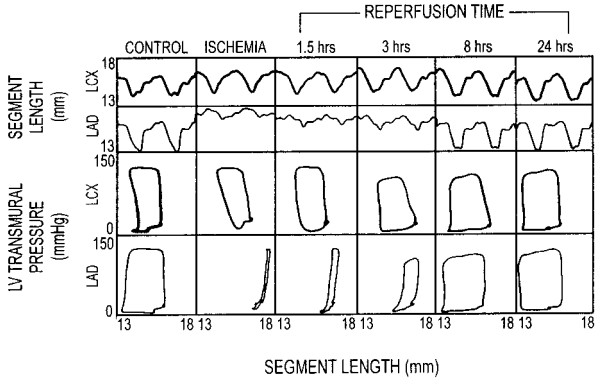

Fig 2. Representative raw data derived from the LAD coronary artery and the LCX myocardial regions are shown for one animal. Segment lengths and LV transmural pressure-segment length work loops in the respective distributions during control conditions, acute ischemia, and after 1.5, 3, 8, and 24 hours of reperfusion document the regional ischemia and gradual recovery within the LAD coronary artery region.

After 24 hours of recovery from ischemia, baseline conditions were confirmed before repeated ischemia was induced. This model has been repeatedly validated as one of reliable recovery from reversible myocardial ischemia.[14-16] Infusion sequence after ischemia was formally randomized such that all 9 animals underwent 3 occlusions and received all 3 infusions during 3 concurrent 24-hour periods. By this method, each animal had a 1-in-3 chance of receiving 1 of 3 infusion sequences.

At study completion, animals were killed according to Duke University guidelines, and autopsies documented correct positioning of implanted hardware. The LV was serially sectioned at 1-cm intervals to ensure that no animals experienced gross myocardial infarction.

Data analysis. Analog data were filtered, digitized in real time by an analog-to-digital converter (ADAC 1012; ADAC Laboratories, Woburn, Mass), and collected on a personal computer–based system. Data analysis was performed on a VAXStation model 4000 (Digital Equipment Corp, Maynard, Mass).

The first-time derivative of LV transmural pressure was computed from the digital pressure waveform as a running 5-point polyorthogonal transformation. The cardiac cycle was defined automatically on the basis of the first-time derivative of LV transmural pressure, as described previously.[14]

Regional stroke work (SW) analog was calculated as the integral of LV transmural pressure (P) and myocardial segment length (L) through each cardiac cycle[15,16]:

$$SW = \int P \, d \, L \qquad \text{(Eq 1)}$$

where d is derivative. SW was regressed against end-diastolic segment length (L_{ed}) to obtain the linear preload recruitable stroke work (PRSW) relationship described by the following equation:[15,16]

$$SW = M_w (L_{ed} - L_w) \qquad \text{(Eq 2)}$$

where M_w and L_w are the slope and x-intercept of the relationship, respectively.

Because reversible myocardial ischemia simultaneously alters M_w and L_w, accurate assessment of contractile function with the use of the PRSW relationship alone is difficult. Therefore, contractile performance was quantified with the use of the preload recruitable work area (PRWA), a normalized index of regional contractile performance. The PRWA incorporates changes in M_w and L_w and represents contractile function as one analyzable variable. PRWA was defined by the area beneath the line described by the PRSW relationship and determined as follows:

$$PRWA = (M_w/2)\,([1.2]\,[L_{wmax}] - [L_w])^2 \qquad \text{(Eq 3)}$$

L_{wmax} is the maximal x-intercept obtained throughout the study of a given animal. The factor of 1.2 was included to ensure that PRWA was always positive, yet diminished significantly as L_w approached L_{wmax}.[15,16]

Hemodynamic variables, PRSW relationships, and PRWA were determined for baseline, acute ischemia, and 1.5, 3, 8, and 24 hours of reperfusion after placebo, CGRP, or nitroglycerin infusions.

Statistics. Steady state data represent mean values over 10 to 20 cardiac cycles. Analysis of variance for repeated measured was used to detect the effects of time, treatment sequence, or treatment type (placebo, nitroglycerin, or CGRP) on hemodynamic parameters and PRWA. For analysis of variance with PRWA, analysis was performed on data after treatment was started (1.5, 3, 8, and 24 hours of reperfusion). Analysis of covariance used the baseline value of PRWA before ischemia to control for the significant differences in baseline values because of different intercrystal distances between animals and because of differences in sonomicrometer tracking between occlusions. Unless otherwise stated, all data are mean ± SD.

Results

Nine animals underwent 3 concurrent episodes of reversible myocardial ischemia and received 1 of 3 infusions after each ischemic period. Three animals did not complete reperfusion from the third occlusion because of hardware malfunction (n = 2 animals) or cardiac arrhythmia (n = 1 animal). Unless otherwise stated, data are presented for the 6 animals that completed 3 studies each.

After LAD coronary artery occlusion and the onset of regional myocardial ischemia, systolic shortening within the ischemic region decreased immediately, worsened to systolic bulging, and slowly normalized during the 24 hours of recovery, as evidenced by the change in segment lengths and depicted in Fig 2. The deterioration in systolic shortening was manifest by the narrowing of the pressure-segment length work loops created in the ischemic LAD coronary artery region (Fig 2). As expected, systolic shortening in the

LCX coronary artery region was unaffected by LAD coronary artery occlusion, and pressure-segment length work loops from the LCX coronary artery region were unchanged after ischemia (Fig 2). These changes in raw data were seen regardless of the infusion used during reperfusion.

Hemodynamic variables including heart rate, mean ejection pressure, LV end-diastolic pressure, and end-diastolic segment lengths were compared during ischemia and reperfusion in the presence of CGRP, nitroglycerin, or placebo (Fig 3). Compared with placebo, CGRP infusion was associated with increased heart rate during infusion ($P < .0001$) and after 8 hours of reperfusion ($P = .04$; Fig 3, *A*). Conversely, nitroglycerin infusion did not significantly alter heart rate at any point that was measured during ischemia and reperfusion ($P > .1$ for all time points; Fig 3, *A*). Both CGRP and nitroglycerin infusions decreased LV end-diastolic pressure (Fig 3, *B*; CGRP, $P = .003$; nitroglycerin, $P = .002$) and mean ejection pressure (Fig 3, *C*; CGRP, $P = .01$; nitroglycerin, $P = .001$) relative to placebo, but these effects were seen during infusion only. Alteration and recovery of end-diastolic segment length were similar after CGRP and nitroglycerin infusions relative to placebo, which implied that discrete changes in regional geometry were similar after each infusion ($P > .3$ for all time points; Fig 3, *D*).

Construction of PRSW relationships between regional stroke work and end-diastolic segment length during ischemia and reperfusion yielded highly linear relationships ($r^2 > 0.90$; $P = .001$) in each animal. After transient regional ischemia, PRSW relationships were typically characterized by an initial decrement in the M_w and an increase in L_w, regardless of the infusion used during recovery (data not shown). Effects of ischemia on M_w and L_w were maximal during acute ischemia and returned toward baseline as reperfusion continued. Similar alterations in M_w and L_w were seen after regional ischemia, irrespective of the infusion used during recovery. Consequently, the order of infusion did not affect PRWA values that were obtained ($P > .2$).

After CGRP infusion, PRWA in the ischemic LAD coronary artery region was significantly increased at each time point of reperfusion relative to placebo and nitroglycerin ($P = .01$, by analysis of covariance), although the raw value of PRWA was greater for CGRP than placebo only at 1.5 hours of reperfusion because of large but insignificant differences in baseline PRWA between treatment groups (Fig 4). To correct for differences in baseline PRWA between treatments, PRWA was also calculated as percent of baseline values (Fig 5). Here the effect of CGRP throughout subsequent reperfusion (detected by analysis of covariance but not visualized in Fig 4) was better detected and visualized throughout subsequent reperfusion ($P = .01$) and for each time point ($P < .05$ for 1.5, 3, 8, and 24 hours; Fig 5). Nitroglycerin had no significant effect on PRWA at any time during reperfusion (Figs 4 and 5). Given no effect of nitroglycerin on PRWA, analysis of covariance was repeated on raw PRWA data for all 8 animals that received complete courses of placebo and CGRP (Fig 6). Here, the effect of CGRP relative to placebo was highly significant throughout subsequent reperfusion ($P = .005$) and for each individual time point ($P < .05$; Fig 6).

In the nonischemic LCX coronary artery region, CGRP did not significantly affect PRWA values relative to placebo throughout reperfusion (Fig 7).

Discussion

Increased understanding of the mechanisms and manifestations of acute coronary syndromes and improvements in managing these syndromes has introduced myocardial stunning as an important issue of cardiac care.[1,3] Common clinical scenarios in which postischemic dysfunction may be encountered include reperfusion after successful PTCA or thrombolytic therapy; after coronary artery bypass grafting, heart transplantation, or other cardiac procedures; and after successful resuscitation from cardiopulmonary arrest.[1,3]

Patients with hemodynamically significant stunning are typically managed with inotropic therapy, which mitigates the functional detriment caused by reversible ischemia until the heart has functionally recovered. However, widespread use of inotropic or vasoactive medications may not always be beneficial because inotropic agents increase myocardial oxygen consumption, increase the risk of arrhythmias, thereby necessitating invasive hemodynamic monitoring, and thus may adversely affect the long-term function of stunned myocardium.[1,15] Therefore, a strategy to augment the performance of stunned myocardium without the subsequent induction of negative functional consequences is attractive and has ready clinical application.

CGRP is an endogenous peptide that exerts chronotropic, inotropic, and vasodilatory properties directly on the myocardium. The role of CGRP in myocardial ischemia has been intensely investigated.[5,6,17-19] In fact, plasma levels of CGRP are increased in patients with acute myocardial ischemia,[7] and Lechleitner and colleagues[9] have recently noted increased endogenous CGRP during coronary artery bypass procedures that are performed without cardiopulmonary bypass. Furthermore, Li and col-

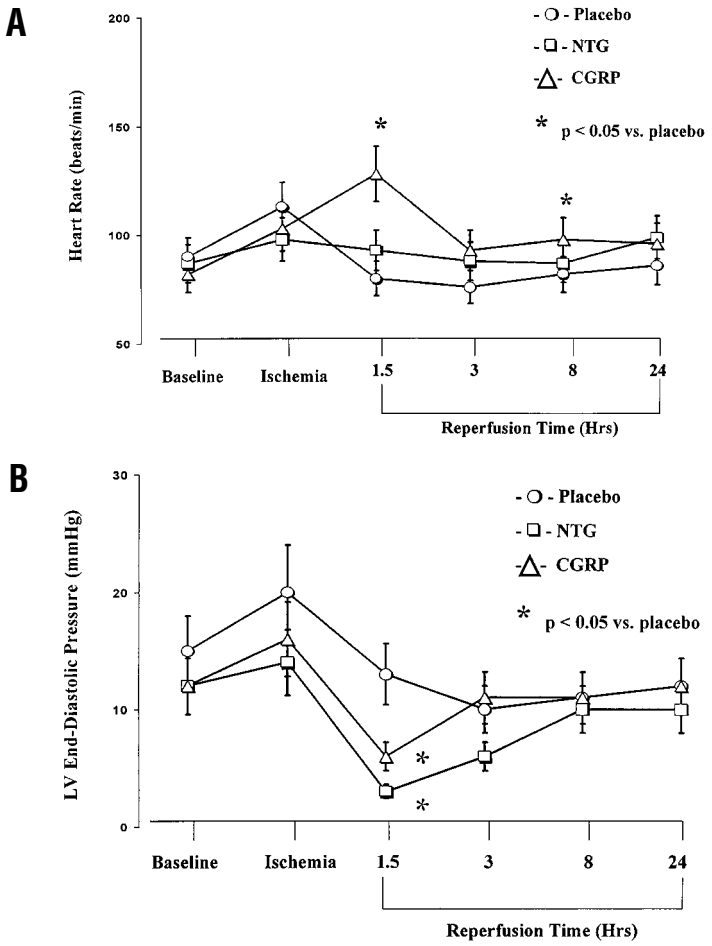

Fig 3. Mean heart rate **(A)** and LV end-diastolic pressure **(B)** for placebo, CGRP, and nitroglycerin (*NTG*) during control conditions, acute ischemia, and 1.5, 3, 8, and 24 hours of reperfusion. *NS*, Not significant.

leagues[20] have reported that isolated rat hearts preconditioned with CGRP have preserved function after ischemia and that preconditioning with CGRP appears to electrically stabilize the myocardium during subsequent ischemia.

However, few reports of exogenous CGRP administration in myocardial ischemia exist. Uren and colleagues[13] infused CGRP in patients with coronary artery disease who underwent exercise treadmill testing and found that CGRP administration was associated with delayed onset of ischemia. In addition, Källner, Gonon, and Franco-Cereceda[21] noted that CGRP infusion after regional myocardial ischemia augmented postischemic coronary artery flow in pigs. Although encouraging, previous investigation of CGRP in myocardial ischemia has lacked assessment of contractile function. The current study represents the first known load-insensitive determination of contractile function after exogenous CGRP infusion in a closed-chest, conscious model of stunned myocardium.

In the current study, contractile function was assessed by means of the PRWA, a normalized index of regional myocardial performance. PRWA is especially useful when serial assessment of regional contractile performance is desired. For example, during episodes of ischemia and reperfusion, simultaneous alterations in the slope and x-intercept of the PRSW relationship preclude accurate statements of performance based on the PRSW relationship alone. However, PRWA incorporates both the PRSW slope and x-intercept to summarize assessment of contractile function.[14,15] In this study, relative to placebo, brief treatment with CGRP significantly improved contractile function (PRWA) in the ischemically injured zone throughout reperfusion (Figs 4, 5, and 6). This effect persisted up to 24 hours of reperfusion in the ischemically injured LAD coro-

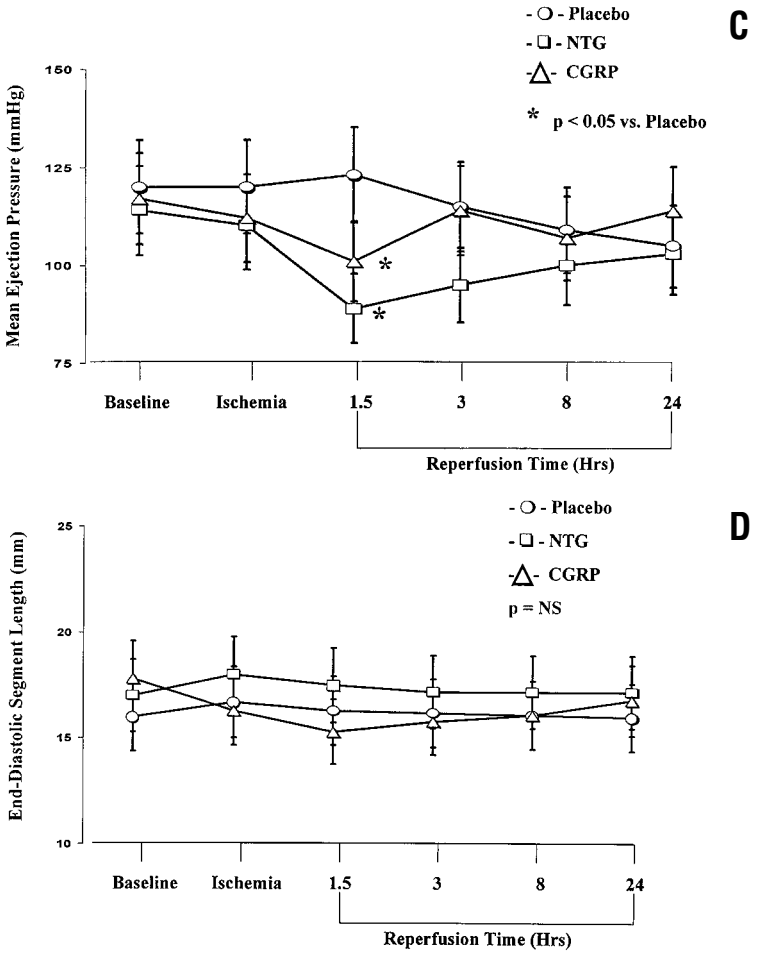

Fig 3. Cont'd. Mean ejection pressure **(C)** and end-diastolic segment length **(D)** for placebo, CGRP, and nitroglycerin (*NTG*) during control conditions, acute ischemia, and 1.5, 3, 8, and 24 hours of reperfusion. *NS,* Not significant.

nary artery zone (Figs 5 and 6), despite the absence of significant residual direct effect of CGRP on contractile function in the uninjured LCX zone after the CGRP infusion was stopped (Fig 7).

These results are important and unique because previous studies have not examined the recovery of function after myocardial ischemia. Several inotropic agents have been evaluated in the general context of myocardial ischemia, yet few data examine the long-term (>1 hour) effects of inotropic stimulation of hearts during ischemia and reperfusion. Kabas and colleagues[15] evaluated conscious dogs after 15 minutes of regional myocardial ischemia followed by reperfusion with either dopamine or saline solution placebo infusion. Myocardial performance was significantly augmented during dopamine infusion; however, catecholamine stimulation of injured myocardium resulted in significantly depressed performance throughout the 22 additional hours of reperfusion. The authors concluded that inotropic stimulation of injured myocardium might interfere with its functional recovery. However, similar findings have not been reproduced clinically, and it is not apparent whether these findings are clinically important. Nevertheless, the current study opposes previously held notions based on the study of Kabas and colleagues that inotropic stimulation of stunned myocardium might ultimately be deleterious.

Several points about the data of the current study are important. For instance, CGRP was associated with increased heart rate during infusion and after 8 hours of reperfusion relative to placebo. However, the chronotropic effects of CGRP do not minimize the importance of the functional results that were reported because PRWA is entirely based on the PRSW relationship. For instance, the PRSW relationship has been repeatedly shown to be independent of heart rate varia-

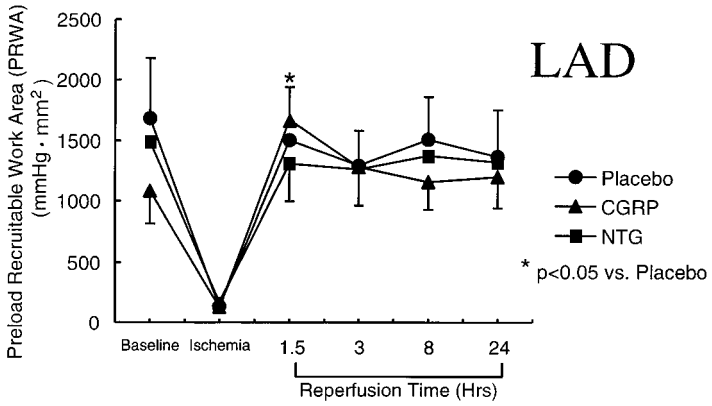

Fig 4. PRWA data (n = 6; mean ± SD) from the ischemic LAD coronary artery region after CGRP or nitroglycerin (*NTG*) infusion compared with placebo. After reversible myocardial ischemia, contractile performance (PRWA) was significantly enhanced by CGRP over all reperfusion (P = .01) and after 1.5 hours of reperfusion (P = .04). Conversely, nitroglycerin did not significantly alter PRWA compared with placebo.

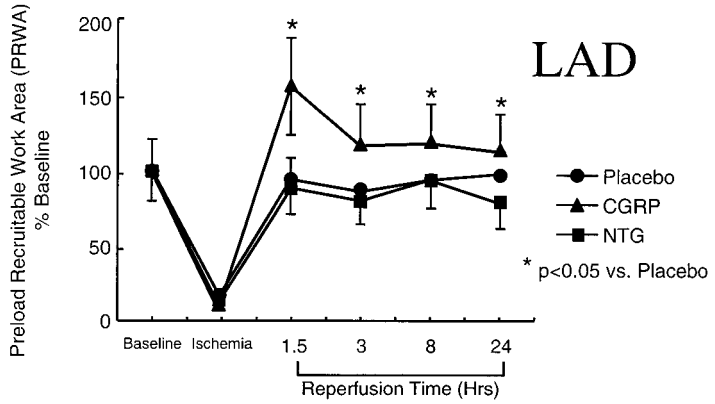

Fig 5. PRWA data (n = 6; mean ± SD) expressed as percent baseline from the ischemic LAD coronary artery region after CGRP or nitroglycerin (*NTG*) infusion compared with placebo. After reversible myocardial ischemia, PRWA was significantly enhanced by CGRP over all reperfusion (P = .01) and at each time in reperfusion (P < .05). Nitroglycerin did not significantly affect PRWA compared with placebo.

tions across a wide physiologic range.[14] In addition, the absolute value of heart rate increase with CGRP was relatively small (<20%), and this degree of increase is not unusual because CGRP is known to exert chronotropic effects on the myocardium.[4,17,19] Still, the long-term effects of CGRP's increased chronotropy on stunned myocardium are uncertain.

Similarly, given the well-described pharmacologic properties of CGRP, the increased PRWA noted in the nonischemic circumflex region is not surprising, and the return of PRWA to baseline levels after completion of the CGRP infusion is consistent with the reported normal half-life of this agent.[22] This finding further suggests that CGRP may confer protective properties on ischemic myocardium relative to normal heart.

The current study was designed to evaluate recovery of myocardial performance after CGRP infusion and cannot offer definitive statements about the molecular mechanisms whereby contractile function is benefited. However, several plausible mechanisms exist by which CGRP may augment performance within stunned myocardium. Depressed contractility within stunned myocardium is often attributed to altered intracellular calcium homeostasis, and evidence suggests that reversible myocardial ischemia impairs the normally sensitive interactions between the contractile apparatus and intracellular calcium.[1,3,23,24] Curiously, CGRP appears to

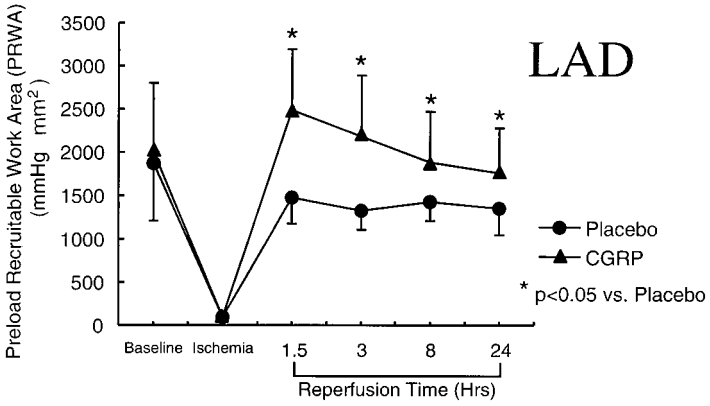

Fig 6. PRWA data (mean ± SD) in the ischemic LAD coronary artery region for all 8 animals that received CGRP infusion compared with placebo. After reversible ischemia, contractile performance (PRWA) was significantly enhanced by CGRP over all reperfusion ($P = .005$) and at each time in reperfusion ($P < .05$).

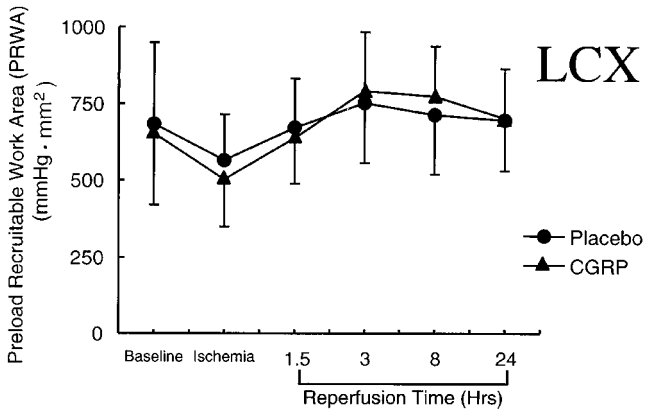

Fig 7. PRWA data (mean ± SD) from the nonischemic LCX coronary artery region after CGRP infusion compared with placebo. PRWA was increased during CGRP infusion; however, PRWA for CGRP and placebo were similar during the remainder of recovery.

affect intracellular calcium balance through activation of the second messenger, protein kinase C.[25,26] Protein kinase C plays an important role in ischemic preconditioning and may influence intracellular calcium homeostasis by a number of mechanisms, including activity at the sarcoplasmic reticulum Ca^{2+} pump or by altering the contractile apparatus to increase Ca^{2+} sensitivity.[27,28] By activating a second messenger (such as protein kinase C), CGRP could induce prolonged, enhanced effects such as those seen in the present study, despite the protein's relatively short half-life.[22] Finally, CGRP may also benefit ischemically injured myocardium as a simple vasodilator. Although vasodilation with nitroglycerin did not duplicate the benefits of CGRP, at least one previous study has observed beneficial effects of vasodilators (dipyridamole and papaverine) not achieved with nitroglycerin in a similar model.[29]

In summary, the administration of CGRP after reversible myocardial ischemia was associated with enhanced recovery of contractile performance within the ischemic region and appears to mitigate the prolonged decrement in contractility typical of stunned myocardium. Given the increased incidence of patients experiencing reversible myocardial ischemia as a result of PTCA, thrombolytic therapy, and surgical revascularization, the potential application of these techniques is far-reaching and may represent an alternative to standard inotropic therapy in these settings.

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